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**DEXAMETHASONE FOR PREVENTION AND TREATMENT
OF ACUTE MOUNTAIN SICKNESS**

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ABSTRACT

We wished to determine in a field study the effectiveness of dexamethasone for prevention and treatment of acute mountain sickness (AMS).

Prevention Trial

We transported fifteen subjects from sea level to 4400m ($P_B = 440$ torr) on Denali (Mt. McKinley) by means of a one hour helicopter flight. In a randomized, double-blind fashion we gave eight subjects a placebo and seven subjects 2mg dexamethasone orally every six hours starting one hour before take-off. The entire placebo group and five of the dexamethasone group developed AMS within five hours, and became progressively more ill until twelve hours when the trial was terminated. We concluded that 2mg of dexamethasone every six hours did not prevent AMS in active soldiers rapidly transported to high altitude.

Treatment Trial

We treated eleven of those with moderate to severe AMS (symptom score 4.5 ± 0.7 , range 3 to 11) with 4mg of dexamethasone every six hours orally or intramuscularly for twenty four hours. All were markedly improved at 12 hours (symptom score 1.0 ± 0.3 p<0.001, range 0 to 3), but symptoms increased after the drug was discontinued at 24 hours (symptom score = 2.4 ± 0.5). We conclude that dexamethasone in a dosage of 4mg PO or IM every six hours is an effective treatment for AMS, but that illness may recur with abrupt discontinuation of the drug.

INTRODUCTION

Acute mountain sickness (AMS) is a common malady afflicting persons ascending quickly to high altitude. Although generally not life-threatening and usually self-limiting, AMS is often incapacitating.^{5,7} Potentially fatal pulmonary and cerebral edema may develop in as many as five to ten percent of those with AMS.⁷ Staged ascent with adequate time for acclimatization is optimal for prevention, but is not always effective and is often impractical. Therefore, pharmacological prophylaxis has been of great interest.

The current agent of choice for prevention of AMS is acetazolamide.^{5,10} However, two recent studies, one hypobaric chamber study and one field study, found dexamethasone also effective in preventing symptoms of AMS.^{9,16} The investigators gave 4mg dexamethasone every six hours starting 48 hours prior to decompression or ascent. The subjects were sedentary.

We considered a clinical trial necessary to determine if a lower dose of dexamethasone, with presumably fewer side-effects, was effective when used for the prevention of AMS in active subjects, a situation more similar to real-life deployment. We also wished to extend the previous observations and study dexamethasone as a treatment for established cases of AMS. We hypothesized that if acute mountain sickness were due to a type of cerebral edema responsive to steroids, then dexamethasone could be of value.

To test these hypotheses, we rapidly transported fifteen soldiers from sea level to 4400m. The studies included a double-blind, placebo-controlled trial of 2mg dexamethasone every six hours starting 1 hour before flight to high altitude; and subsequently a trial of 4mg dexamethasone every six hours for the treatment of AMS. We found that the lower dose dexamethasone did not prevent AMS in active soldiers, and that the higher dose of dexamethasone was an effective treatment for those ill with AMS.

METHODS

The test subjects were fifteen healthy military men on no medication, age 28 ± 1.0 , height(cms) 181 ± 2 , and weight(kgs) 83 ± 4 . None had been to high altitude within three weeks before the study. All subjects gave informed consent.

Setting

All high altitude studies were completed in a heated (15 degrees C) laboratory shelter (Weatherport, Gunnison, CO) on a glacier at 4400m, on the West Buttress Route of Denali (Mt. McKinley). The average

ambient barometric pressure was 435 ± 1.0 torr and the ambient temperature ranged from -40 degrees C (night) to 0 degrees C (daytime).

Measurements

We made baseline measurements on two separate days in Talkeetna, Alaska ($P_B = 752$ torr). We repeated them once 12 hours after arrival at altitude for the prevention trial, and every 24 hours after arrival for three days for the treatment trial. Measurements included body weight, minute ventilation (V_E) and forced vital capacity (FVC) measured with a turbine spirometer (Boehringer Laboratories, Wynnewood, PA), peak expiratory flow measured with a mini-Wright's peak flow meter (Clement Clark, Ltd., England), and blood oxygen saturation and heart rate from a portable pulse oximeter (Nelcor N-10, Hayward, CA).

Symptom Scores

One investigator rated the severity of AMS symptoms and made a functional assessment at the same time the measurements were made, using a modified interview and examination technique.^{5,6} The scoring system is presented in Table I. As in previous work, an AMS symptom score of 2 or greater was diagnostic of AMS.^{5,6} In the text, AMS symptom score refers to the clinical score unless otherwise noted. Time of onset of each symptom was also recorded. To compare symptom severity to other studies, subjects completed a self-report questionnaire, the Environmental Symptom Questionnaire, and cerebral (AMS-C) and respiratory (AMS-R) scores were obtained.¹⁷ Sampson et al. report that an AMS-C score of 0.7 and an AMS-R score of 0.6 reliably represent persons who report being sick.¹⁷

Prevention Trial Protocol

To field-test the effectiveness of dexamethasone for the prevention of AMS the fifteen subjects were randomized to receive either placebo ($n=8$) or 2mg dexamethasone ($n=7$) every six hours in a double-blind fashion, starting one hour before flying by helicopter to high altitude. The subjects arrived at 4400m at approximately 1230, after flying from Talkeetna in one hour. On arrival at 4400m, they spent the first six hours erecting tents, building snow walls and igloos, carrying heavy loads, and performing other camp chores. All were given the same diet, but no attempt was made to control water or caloric intake. Subjects were not permitted to use any self-prescribed drugs during the study. Within twelve hours of arrival at 4400m, at the

time of the first measurements at altitude, the subjects were too ill to continue, and for ethical concerns and safety reasons we terminated the prevention trial.

Treatment Trial Protocol

To evaluate the effectiveness of dexamethasone for treatment of established AMS, we gave subjects with AMS 4mg of dexamethasone PO every six hours for twenty four hours. Eleven of the thirteen subjects with AMS volunteered for the treatment study; four had been on the lower dose dexamethasone, seven had been on placebo. We chose not to have a control group because all subjects were becoming progressively more ill, and two already had severe illness. Therefore, we considered it unethical that any of these subjects be randomized into a placebo group. Adequate oxygen or evacuation to a lower altitude was available in the event that any subjects deteriorated further. Treatment was started at 2200 to 2400 hours, approximately twelve hours after arrival. Because of progressive neurological deterioration, two severely ill subjects received oxygen (3 l/min via nasal cannula), but only for 30 to 60 minutes, concurrent with receiving 4mg dexamethasone intramuscularly. In addition, another subject was given a single dose of 10mg intramuscular prochloroperazine (Compazine) and 4mg dexamethasone PO as above. No other medications were given during the 24 hour dexamethasone treatment trial.

Statistics

Physiological differences between placebo and dexamethasone during the prevention study were evaluated by the Student's t-test with Bonferroni's correction for multiple tests. Differences in physiological measures during the treatment study were evaluated by analysis of variance for repeated measures, using Scheffe's test for post-hoc comparisons. All symptom score comparisons were completed using the Mann-Whitney U-test. In all comparisons $p < 0.05$ was considered significant. Means \pm S.E.M. are presented in the text.¹

RESULTS

Prevention Trial

At sea level, the placebo and dexamethasone groups were similar with respect to all demographic and physiologic variables. On ascent to high altitude, symptoms of AMS developed quickly; mean time to first symptoms of AMS for all subjects was 2.3 ± 0.3 hours, range 0.5 to 5 hours. All eight in the placebo group and

five of seven in the dexamethasone group (13 total) had AMS as defined both by clinical AMS symptom scores of 2 or greater, and Environmental Symptoms Questionnaire derived AMS-C values of 0.7 or greater. The mean clinical AMS symptom scores were not significantly different between the two groups (2.6 ± 0.6 , range 0 to 4, for the dexamethasone group compared with 4.6 ± 1.0 , range 2 to 11, for the placebo group, $p=0.09$). Two subjects on placebo developed severe AMS with progressively severe headache, vomiting, ataxia, lassitude requiring assistance (prostration), and deterioration in consciousness, while none were as severely ill in the dexamethasone group. We terminated the prevention study twelve hours after arrival at altitude because of progressing illness. At that time subjects were due for the third dose of the drug. Of the two subjects on dexamethasone who felt well, one went on to develop severe AMS thirty six hours after the medication had been stopped, the other remained well off medication.

We observed the following physiologic changes twelve hours after ascent with no significant differences between dexamethasone and placebo groups or with symptom score: $\text{SaO}_2\%$ decreased from $96 \pm 0.2\%$ to $74 \pm 2\%$, heart rate increased $32 \pm 6.0\%$ to 98 ± 4 beats per minute, peak flow decreased $17 \pm 2.5\%$ to 514 ± 55 l/min, and V_E increased $84 \pm 34\%$ to 12.4 ± 2 l/min.

Treatment Trial

Symptom score was significantly improved after two doses of 4mg dexamethasone given at six hour intervals ($p<0.01$). Ten of the eleven subjects had markedly improved, eight of whom no longer reached the criteria for AMS, and five of these eight had no symptoms at all. Most subjects noted improvement within four hours after the first dose. We discontinued the drug after five doses (twenty four hours) and repeated measurements the next two days. The first morning after the drug was stopped (twelve hours later) only three persons had any symptoms, and only one had AMS, with a symptom score of 2. On the second day, however, six persons had symptoms, and four had AMS.

$\text{SaO}_2\%$ increased as illness resolved ($73.1 \pm 1.7\%$ to $77.3 \pm 0.9\%$ after 12 hours and $81.4 \pm 1.5\%$ after 36 hours $p<0.05$). Peak expiratory flow also increased from 495.5 ± 22 l/min to 540 ± 19 l/min at 12 hours and to 560 ± 18 l/min at 36 hours ($p<0.01$).

DISCUSSION

We found that i) 2 mg dexamethasone taken every six hours starting one hour before rapid ascent to high altitude did not prevent AMS in active soldiers; ii) 4mg dexamethasone given every six hours was an effective treatment for AMS; and iii) AMS may start or recur when dexamethasone is discontinued.

None of the subjects reported important problems attributable to dexamethasone. Minor subjective side-effects such as increased libido, bizarre daydreams and dreams were noted, and a transient depression occurred in one subject three days after discontinuing dexamethasone. Gastrointestinal symptoms occurred in only 3 of 7 in the dexamethasone group compared to 7 of 8 in the placebo group suggesting that such symptoms were due to AMS rather than dexamethasone.

Prevention Trial

The ineffectiveness of dexamethasone for prevention of AMS was surprising and has a number of possible explanations. We used a lower dose than Johnson *et al.*⁹ and Rock *et al.*¹⁶, and gave the drug only one hour before altitude exposure. The fact that subjects had become more ill after repeated low doses and suddenly improved with the higher dose suggests that the initial dose was insufficient, rather than that it was given too late. Also, it may be that active persons require the higher dose because of the increased hypoxic stress. The soldier's level of exertion may be one reason AMS was twice as severe in our study (AMS-C = 2.1) as in those subjects exposed to a similar barometric pressure in both a chamber study (AMS-C = 1.09) and on Pike's Peak (AMS-C = 0.8). Two mg may be effective in sedentary persons. We must also consider the possibility of a type II error, namely that if there had been a larger number in each group, a statistically significant advantage for dexamethasone might have emerged. Indeed, dexamethasone seems to have prevented the severe illness observed in the placebo group. The data thus suggest a partial beneficial effect of 2mg dexamethasone; presumably a higher dose would be more effective.

Treatment Trial

The improvement in AMS symptom score after treatment with two doses of 4mg of dexamethasone (and in some cases one dose) was impressive. It is possible that some of the improvement in the two severely ill subjects was due to the brief period of breathing oxygen, due in all subjects to improved acclimatization with time at altitude, or due to a placebo effect. We know from previous trials, however, that oxygen breathing for

thirty to sixty minutes is generally of benefit only during its use.⁸ Symptoms quickly return to pre-treatment severity when oxygen is used so briefly. And, since arterial oxygen saturation returned to pre-treatment values within minutes of discontinuing the oxygen, a significant role for oxygen in the sustained improvement of these two subjects while on dexamethasone is doubtful. Secondly, even if we were to exclude these subjects, the improvement in symptom scores associated with dexamethasone was still significant (from 3.4 ± 0.2 to 0.8 ± 0.4 , $p < 0.01$).

Twelve hours of acclimatization may have helped to reduce symptom scores. However, in circumstances of rapid deployment of troops similar to the present study, Singh et al. determined the average duration of acute mountain sickness to be two to five days.¹⁹ Johnson and colleagues found a slight improvement in AMS only after 24 hours of hypobaria (Dr. Paul Rock, US ARIEM, November 1986, personal communication). Given the severity of the illness in our study, the fact that the AMS was becoming progressively worse, and the natural history of the illness, it is most likely that the subjects would have become more ill over the next twelve hours if they had not been on dexamethasone. Finally, the fact that six of the eleven developed more symptoms after the drug was stopped also suggests that dexamethasone was the cause of the initial improvement.

Steroids were first suggested for treatment of altitude illness by Singh et al.¹⁹ In nineteen subjects with "incapacitating AMS" given betamethasone in conjunction with furosemide, these investigators found that the drugs relieved headache and vomiting within three days. Although they stated that each drug alone was "highly effective", they did not report the results of betamethasone alone. To our knowledge no other studies were published on the subject until the chamber study of Johnson et al. in 1984⁹ followed by a field study in 1987.¹⁶ Our finding that 4mg dexamethasone reversed AMS under field conditions reinforces these studies which showed that the same dose was effective for preventing AMS.

Our results also support the beneficial effect of dexamethasone noted in an anecdotal case report,³ and in a new study from the Alps.² Ferrazzini et al. studied dexamethasone in a controlled fashion with subjects nearly as ill as ours, and found the same prompt reduction in symptoms, using an initial dose of 8mg, followed by 4mg every six hours.² We agree that descent is still to be regarded as the treatment of choice for severe mountain sickness,¹⁸ but dexamethasone may offer valuable adjunctive therapeutic benefit. One of the authors (PH) has used dexamethasone in the treatment of many cases of high altitude cerebral edema with coma and,

like Shlim,¹⁸ has not found it particularly effective. Dexamethasone may be useful only in the earlier stages of cerebral edema; i.e. in moderately severe acute mountain sickness.

The exact mechanism by which dexamethasone may act in this setting is unclear. Dexamethasone may improve blood-brain barrier integrity and therefore reduce edema as it does in vasogenic edema associated with brain tumors.^{4,11} Recent work with a rat glioma model showed that the anti-inflammatory effect of dexamethasone was responsible for suppression of edema, since both steroids and non-steroidal anti-inflammatory agents were effective.¹⁵ Meehan,¹³ however, found the anti-inflammatory naproxen ineffective for prevention of AMS, suggesting that steroids may work for AMS by a mechanism other than their anti-inflammatory effect. Dexamethasone is known to treat nausea and vomiting,¹² but this effect alone could not account for the improvement in clinical symptom scores. Johnson and colleagues found less retinal vasodilatation in the treated group, suggesting dexamethasone had vasoconstrictive action, but it was not clear if this was a cause or effect.⁹ Regardless of the mechanism, it appears that dexamethasone dosage for successful treatment of high altitude illness is in the higher range used to treat edema rather than in the range used to treat inflammation.

In summary, we performed a study on the efficacy of dexamethasone for prevention and treatment of acute mountain sickness in subjects rapidly deployed to 4400m on Denali. Two mg dexamethasone did not prevent AMS in active subjects, while four mg every six hours effectively treated AMS. Sixteen mg of dexamethasone daily did not seem to aid acclimatization, since discontinuing the drug resulted in recurrence of illness. We conclude that dexamethasone may be a safe and effective treatment for established cases of acute mountain sickness.

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Table I. AMS Symptom Questionnaire.^{5,6}

SYMPTOM	SCORE	REMARKS
Headache	1	transient, relieved with analgesic
	2	severe, or not relieved with analgesic
Insomnia	1	difficulty falling asleep, frequent waking
Dizziness	1	
Ataxia	1	difficulty maintaining balance
	2	steps off line
	3	falls to ground or cannot finish test
Severe Lassitude	3	requires assistance for tasks of daily living
Anorexia or nausea	1	true anorexia, not distaste for diet
Vomiting	2	
Dyspnea on Exertion	2	dyspnea forces frequent halts, slow to recover
At Rest	3	marked dyspnea at rest
Global Functional Assessment	0	no symptoms
	1	symptoms, but able to continue
	2	symptoms, stopping ascent
	3	intensive medical treatment and/or evacuation to lower altitude required

Table II. Symptom scores in eleven subjects during and immediately following dexamethasone treatment. We gave 4mg dexamethasone (DX) at 0, 6, 12, 18 and 24 hours, and made measurements at 0, 12, 36, and 60 hours. Values are means \pm S.E.M.

DEXAMETHASONE TREATMENT				
TREATMENT	BEFORE	ON DX	POST	
HOURS OF STUDY	0	12	36	
AMS Symptom Score ¹	4.46 ± 0.7	$1.0 \pm 0.4^+$	$0.4 \pm 0.2^+$	$1.2 \pm 0.4^+$
Rough Functional Assessment ¹	1.6 ± 0.2	$0.6 \pm 0.2^+$	$0.2 \pm 0.1^+$	$0.5 \pm 0.2^+$
AMS-C ²	2.1 ± 0.2	$0.6 \pm 0.3^+$	$0.2 \pm 0.1^+$	$0.3 \pm 0.1^+$
AMS-R ³	0.96 ± 0.2	$0.4 \pm 0.1^+$	$0.2 \pm 0.1^+$	$0.5 \pm 0.2^*$

⁺ p<0.01 versus before treatment; * p<0.05 versus before treatment.

¹ AMS symptom score and rough functional assessment derived from clinical interview.^{5,6}

² AMS-C scores were derived from the Environmental Symptoms Questionnaire. AMS-C represents responses to questions about the following symptoms: feel sick, faint, hungover, weak, dizzy, coordination off, vision dim, lightheaded, headache, loss of appetite, nausea.¹⁷

³ AMS-R scores were derived from the Environmental Symptoms Questionnaire. AMS-R represents responses to questions about the following symptoms: hard to breathe, hurts to breathe, stomach ache, nausea, depressed, couldn't sleep, headache, stomach cramps, back aches, nose stuffed, nose bleeds.¹⁷

Figure Legends

Figure 1. A view of the upper Southwest side of Denali (Mt. McKinley) showing (X) the location of the high altitude laboratory (4400m), and part of the trail (—) used by climbers to reach the camp.

Figure 2. Acute mountain sickness symptom score was significantly decreased with dexamethasone (DX) treatment. Note the rebound effect after discontinuation of dexamethasone.